UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/724,292 | 12/01/2003 | Juan Armendariz Borunda | 061537-0036US | 4513 |

9629 7590 01/15/2009
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

| EXAMINER | |
|---|---|
| CHEN, SHIN LIN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 01/15/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/724,292 | ARMENDARIZ BORUNDA ET AL. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *22,24,28-30 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24,28-30 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-31-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-28-08 has been entered.

Applicants' amendment filed 10-28-08 has been entered. Claims 22 and 24 have been amended. Claims 22, 24, 28-30 and 32-34 are pending and under consideration.

***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 22, 24, 28-30 and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "wherein the composition is suitable for intravenous administration" in claim 22 is vague and renders the claim indefinite. It is unclear what kind of composition is "the composition suitable for intravenous administration". It is unclear as to the metes and bounds of what would be considered "suitable for intravenous administration". The specification fails to define such composition. Claims 24, 28-30 and 32-34 depend from claim 22 but fail to clarify the indefiniteness.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22, 24, 28-30 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "wherein the composition is suitable for intravenous administration" in claim 22 is considered new matter. Applicants fail to point out where the support is in the specification for the phrase "wherein the composition is suitable for intravenous administration". There is no support for a composition that is suitable for intravenous administration. The specification fails to provide sufficient support for the phrase set forth above. Thus, the phrase "wherein the composition is suitable for intravenous administration" is considered new matter.

Applicants cite paragraphs [0023] and [0024] of the specification and argue that the specification support the concept that the adenoviral vectors can be injected intravenously (amendment, p. 4). This is not found persuasive because of the reasons set forth above. The specification might have support for the concept of intravenous injection of adenoviral vector, however, there is no support in the specification for a composition that is suitable for intravenous administration.

6. Claims 22, 24, 28-30 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing fibrosis in hepatic cirrhosis by injecting via iliac vein a replication defective adenovirus vector AdMMP-8 expressing human MMP-8 protein under the control of CMV promoter as disclosed in the cited references Siller-Lopez et al., 2004 (Gastroenterology, Vol. 126, p. 1122-1133) and Garcia-Banuelos et al., 2002 (Gene Therapy, Vol. 9, p. 127-134) (amendment filed on 10-31-07), does not reasonably provide enablement for a pharmaceutical composition comprising recombinant adenovirus expressing the proteins as recited in the claims under the control of various promoters, and a method for treating various fibrotic disorders in a human patient by using said pharmaceutical composition via intravenous administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 22, 24, 28-30 and 32-34 are directed to a pharmaceutical composition comprising a therapeutically effective amount of unitary doses of viral particles of recombinant adenoviral vectors containing a DNA sequence encoding a human MMP protein under the control of a ubiquitous promoter, a tissue-specific promoter or a combination thereof, for the treatment of human hepatic fibrosis and a pharmaceutically acceptable carrier, and a method of treating fibrotic disorders, such as hepatic fibrosis, pulmonary fibrosis, renal fibrosis, keloids, hypertrophic scars, or combination thereof, in a human patient by delivering a recombinant adenoviral vector expressing therapeutic proteins via an administration route to an organ. Claims 28-30 and 32-34 specify the therapeutic protein for the treatment of hepatic fibrosis is MMP-8, MMP-1, truncated receptor for TGF-beta type II, MMP-2, MMP-9 and MMP-13, respectively.

The specification discloses that the rat models, including healthy rats, rats intoxicated with carbon tetrachloride (CCl4) and rats with ligation of the bile duct (LCB), receive infusion of Ad5gal vector by iliac vein shows that the main target organ of the infused adenoviral vector is the liver. The spleen and the lung present a transduction grade lower than 1% and other organs, such as kidney, heart and brain, show no transduction at all (specification, pages 12-16).

The specification states "[t]he present invention relates to the creation of RECOMBINANT ADENOVIRAL vectors bearing exogenous genes that encodes for therapeutic

proteins useful in the treatment of HEPATIC cirrhosis and generalized FIBROSIS, such as renal FIBROSIS, pulmonary FIBROSIS, HYPERTROPHIC scars and keloid of the skin, and/or in other target organs susceptible to suffer from it" and "the invention provides an effective way for the treatment of fibrosis through the employment of recombinant adenoviral vectors which are claimed here, as well as the process to prepare these vectors, the pharmaceutical composition that contains them, and their therapeutic uses in the treatment of several fibrosis" (specification, page 1, first and second paragraphs). The "pharmaceutical composition" implies therapeutic use of said composition. Thus, the claims read on gene therapy for the treatment of various fibrotic disorders in vivo.

The claims encompass treating various fibrotic disorders, such as hepatic fibrosis, in a human patient by delivering a recombinant adenoviral vector expressing a therapeutic protein, such as MMP-1, MMP-2, MMP-8, MMP-9, MMP-13 and truncated receptor for TGF-beta type II, under the control of a promoter to liver via intravenous administration in vivo. The specification fails to provide adequate guidance and evidence for delivering a recombinant adenoviral vector expressing any therapeutic protein under the control of a promoter via intravenous administration in vivo such that sufficient therapeutic protein can be obtained so as to provide therapeutic effects in target organs for treating any fibrotic disorder, such as hepatic fibrosis, in a human patient with the exception of the disclosed references cited in the amendment filed on 10-31-07, i.e. references Siller-Lopez et al., 2004 (Gastroenterology, Vol. 126, p. 1122-1133) and Garcia-Banuelos et al., 2002 (Gene Therapy, Vol. 9, p. 127-134).

The claims read on gene transfer and gene therapy in vivo. The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly

unpredictable at the time of filing. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain, M., 1998 (Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma et al., Sept. 1997 (Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3). The adenoviral vector can induce both cell-killing "cellular" immune response and the antibody-producing "humoral" immune response from the host. The virally infected cells can be killed by cytotoxic T lymphocytes and the humoral response results in the generation of antibodies against adenoviral proteins. "There are considerable

immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression" (e.g. p. 241, left and middle column).

Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) reports that numerous factors complicate in vivo gene therapy with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e,g, bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).

The claims also encompass using nucleotide sequences encoding various therapeutic proteins for treating various fibrotic diseases or disorders in a patient. However, different therapeutic proteins have different amino acid sequences and their biological functions would

differ. The specification fails to provide adequate guidance and evidence for whether the claimed therapeutic protein would be able to treat various fibrotic diseases or disorders, such a hepatic fibrosis, in vivo. It was known in the art that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Davis, C. G., 1990 (The New Biologist, Vol. 2, No. 5, p. 410-419) reports that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid contexts, i.e. different proteins.

Further, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for

unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention and even same short stretch of amino acid sequence can show diverse biological functions while surrounded by different background amino acid sequences. It is noted that a truncated receptor for TGF beta II encompass various structural variants of TGF beta II receptor. The truncation could mean one amino acid deletion to deletion of the whole TGF beta II receptor sequence and it represents numerous different protein sequences. The biological function of the "truncated receptor for TGF-beta type II" would be unpredictable from mere amino acid sequence at the time of the invention. The specification fails to provide adequate guidance and evidence for whether the claimed adenoviral vector expressing the recited human MMP proteins or various truncated receptor of TGF beta II would be able to provide therapeutic effect via intravenous administration in vivo so as to treat various fibrotic disorders, such as hepatic fibrosis. Therefore, one skilled in the art at the time of the invention would not know how to use the claimed adenoviral vector to treat various fibrotic disorders in vivo.

In view of the unpredictable nature of gene therapy in vivo, the limitation of using adenoviral vectors in gene delivery, and the unpredictable biological function of a protein from mere amino acid sequence, one skilled in the art at the time of the invention would not know how to use the recombinant adenoviral vector expressing the recited therapeutic protein for treating various fibrotic disorders, such as hepatic fibrosis, in a human via intravenous

administration routes in vivo. One of skilled in the art would require trial and error experimentation to determine the biological function of various therapeutic proteins, preparation of adenoviral vectors expressing various therapeutic proteins, administration of said viral vectors into a subject via intravenous administration, trial and error experimentation to determine whether sufficient therapeutic protein is expressed at the target organ via intravenous administration, and trial and error experimentation to determine whether the expressed therapeutic protein can provide therapeutic effect for treating various fibrotic disorders, such as hepatic fibrosis in a human.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicants cite Example 2 and argue that the specification provides a blueprint for making and using various embodiments of the invention and discloses intravenous administration of adenovirus expressing MMP-8 results in high expression levels of protein. The proteins listed in the claims are known to be useful for collagen degradation, which in turn, can be useful for treating fibrosis. The statement of "lack of evidence" in Office action is improper (amendment, p. 4-5). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph. Usefulness for collagen degradation does not mean that those

recited proteins would be able to treat various fibrotic disorders, including hepatic fibrosis, in vivo. Different proteins have different amino acid sequences and their biological functions would differ. The biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention. The specification fails to provide adequate guidance and evidence for whether sufficient therapeutic protein can be obtained at the target organ via intravenous administration and whether the claimed therapeutic protein would be able to treat various fibrotic diseases or disorders, such a hepatic fibrosis, in vivo.

Applicants cite post-filing references Bramson et al.; Salgado et al.; Weitzman, M.; and Lieber et al., and argue that one skilled in the art could read the present specification and make and use the claimed invention (amendment, p. 6). This is not found persuasive because of the reasons set forth above. The cited references discuss the adenovirus-mediated gene delivery of urokinase plasminogen activator to induce liver regeneration or to revert liver cirrhosis, which use different protein for different purpose and is irrelevant to the instant invention. The gene therapy for treating a disease has to be considered individually because of the unpredictability of the art.

### *Claim Rejections - 35 USC § 103*

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 22 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fernandez et al., 1998 (Surgery, Vol. 124, p. 129-136) in view of Bilbao et al., 2002 (US Patent No. 6,436,393) and Hasty et al., 1990 (The Journal of Biological Chemistry, Vol. 265, No. 20, pp. 11421-11424).

Claims 22 and 28 are directed to a pharmaceutical composition comprising a therapeutically effective amount of unitary doses of about $1x10^7$ pfu to $1x10^{14}$ pfu viral particles of recombinant adenoviral vectors containing a DNA sequence encoding a therapeutic protein under the control of a ubiquitous promoter, a tissue-specific promoter or a combination thereof, for the treatment of hepatic fibrosis in a human and a pharmaceutically acceptable carrier, wherein the therapeutic protein is human MMP-8.

Fernandez teaches preparation of a recombinant adenovirus vector AdMMP-3 expressing MMP-3 protein under the control of CMV promoter and use of said adenovirus vector for ex vivo transfection of human saphenous vein grafting (hSVG) at a dose of $1x10^9$ pfu for studying modulation of MMP activity in hSVG (e.g. abstract, p. 130). Fernandez shows that adenovirus-mediated gene delivery is limited to the vessel's intima and strategy to infect medial smooth

muscle cells need to be developed (e.g. abstract). The dose of $1x10^9$ pfu is in the range of $1x10^7$ pfu to $1x10^{14}$ pfu. The buffer solution containing the adenovirus vector is considered a pharmaceutically acceptable carrier. The term "pharmaceutical" does not carry weight in 35 U.S.C. 103(a) rejection.

Fernandez does not specifically teach the use of adenoviral vector type 5 with E1 deletion and the nucleotide sequence of MMP-8 gene.

Bilbao teaches preparation of an adenoviral vector encoding a human anti-apoptotic Bcl-2 gene under the control of a CMV promoter, wherein the adenoviral vector is type 5 with E1 deletion, and said adenoviral vector can be used for gene therapy of reperfusion injury (column 9, lines 8-13, column 23, lines 28-39).

Hasty teaches the cDNA sequence encoding the human neutrophil collagenase, i.e. MMP-8 (e.g. abstract, Figure 1).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to generate a composition comprising a recombinant adenoviral vector type 5, comprising E1 deletion, expressing a human MMP-8 protein under the control of CMV promoter because Fernandez teaches preparation of an adenoviral vector containing the gene sequence of MMP-3 under the control of CMV promoter for studying modulation of MMP activity in hSVG, Bilbao teaches preparation of adenoviral vector type 5 with E1 deletion for gene therapy, Hasty teaches the cDNA sequence encoding the human neutrophil collagenase (MMP-8), and MMP-8 is a member of MMP family. It would be obvious to one of ordinary skill to substitute the gene sequence of MMP-3 as taught by Fernandez with the cDNA sequence of human MMP-8 as taught by Hasty because they both are members of MMP family.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to study modulation of MMP activity and expression of MMP in hSVG as taught by Fernandez or to prepare an adenoviral vector type 5 with E1 deletion for gene therapy of reperfusion injury as taught by Bilbao with reasonable expectation of success.

Applicants argue that the Office use the phrase "to treat liver fibrosis" as a limitation when examining for enablement purposes but disregarding the limitation when examining for obviousness purposes. Applicants request clearance for the difference in interpretation (amendment, p. 7). It is noted that for art rejection of a product claim, such as claims 22, 28-30 and 32-34, the intended use of the product is irrelevant. The claims are anticipated or render obvious as long as the prior art teaches the components of the product and a motivation to prepare the product. In this case, the components of the claimed pharmaceutical composition are E1 deleted type 5 adenoviral vector comprising a DNA sequence encoding a recited human MMP protein under the control of a ubiquitous promoter or a tissue-specific promoter or combination thereof, wherein the adenoviral vector is in a unitary dose of about $1x10^7$ pfu to $1x10^{14}$ pfu. The cited references Fernandez, Bilbao and Hasty teach all the elements of the claimed product and the motivation to prepare said product. On the other hand, when an enablement issue is considered, the intended use of the claimed product has to be put into consideration because the product must have a patentable use. In this case, the intended use of the product is to treat hepatic fibrosis in a human and this use has to be considered in examining the enablement issue.

Applicants argue that the Office action fails to cite any reference that teach serotype Ad5 and deletion of E1 region (amendment, p. 7). This is not found persuasive because of the reasons

set forth above under 35 U.S.C. 103(a). Bilbao teaches preparation of an adenoviral vector encoding a human anti-apoptotic Bcl-2 gene under the control of a CMV promoter, wherein the adenoviral vector is type 5 with E1 deletion,

Applicants argue that Fernandez does not teach intravenous administration of an adenovirus and Hasty does not cure this deficiency. The Office action states "MMP-1, 2, 8, 9, 13 … are different proteins and have diverse biological functions", therefore, it would not be obvious to substitute MMP-8 for MMP-3 and one skilled in the art would not have reasonable expectation of success in substituting MMP-8 for MMP-3 (amendment, p. 7-8). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 103(a) and the reasons set forth above. As discussed above, the intended use of the product is irrelevant for art rejection of a product claim. However, when an enablement issue is considered, the intended use of the claimed product has to be put into consideration because the product must have a patentable use. Intravenous administration is irrelevant to the obviousness of the claimed product. One of ordinary skill in the art would not have any difficulty in preparing an adenoviral vector expressing various human NNP proteins under the control of a promoter. However, whether an adenoviral vector expressing various human MMP proteins under the control of a promoter would be able to treat hepatic fibrosis in humans was unpredictable at the time of the invention and it depends on the biological function of the human MMP protein used. Therefore, when examining an enablement issue, the diverse biological functions of various human MMP proteins have to be considered but when considering preparation of a product, it would be obvious for one of ordinary skill to substitute on MMP with another MMP with reasonable expectation of success.

10. Claims 22 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al., 1996 (Matrix Biology, Vol. 15, pp. 383-395).

Claims 22 and 33 are directed to a pharmaceutical composition comprising a therapeutically effective amount of unitary doses of about $1x10^7$ pfu to $1x10^{14}$ pfu viral particles of recombinant adenoviral vectors containing a DNA sequence encoding a therapeutic protein under the control of a ubiquitous promoter, a tissue-specific promoter or a combination thereof, for the treatment of hepatic fibrosis in a human and a pharmaceutically acceptable carrier, wherein the therapeutic protein is human MMP-9.

Baker teaches preparation of an adenoviral vector containing the gene sequence of MMP-9 under the control of CMV promoter (abstract, p. 385). Baker further teaches that increased secretion of MMPs is implicated in many pathological conditions, including rheumatoid arthritis, restenosis and atherosclerosis etc. "Clear definition of the normal and pathological function of individual MMPs will benefit from approaches that use gene transfer to produce increases in MMP levels that mimic those observed in pathological conditions" (e.g. abstract).

Baker does not teach the dose of $1x10^7$ pfu to $1x10^{14}$ pfu.

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to generate a recombinant adenoviral vector expressing a MMP-9 protein under the control of CMV promoter with dose of $1x10^7$ pfu to $1x10^{14}$ pfu because Baker teaches infecting cells with multiplicity of infection (MOI) of 0, 3, 30, 100, 300 or 1000 pfu/cell and determining effective dose is routine optimization of a result-effective variable and is obvious to one of ordinary skill.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to obtain effective dose to optimize the effect of the recombinant adenoviral vector with reasonable expectation of success.

Applicants reiterate the difference in enablement rejection and the obviousness rejection in Office action and Baker does not teach intravenous administration of the adenovirus (amendment, p. 8-9). This is not found persuasive because of the reasons set forth above.

Applicants argue that some of the foreign counterparts, EP 1221490, JP4173663 etc., to the present application are patentable (amendment, p. 10). This is not found persuasive because of the reasons set forth above and that the instant application has to follow the US standard and guideline for patentability examination.

11. Claims 22 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al., 1996 (Matrix Biology, Vol. 15, pp. 383-395) in view of Brinckerhoff et al., 1987 (Journal of Clinical Investigation, Vol. 79, p. 542-546).

Claims 22 and 29 are directed to a pharmaceutical composition comprising a therapeutically effective amount of unitary doses of about $1x10^7$ pfu to $1x10^{14}$ pfu viral particles of recombinant adenoviral vectors containing a DNA sequence encoding a therapeutic protein under the control of a ubiquitous promoter, a tissue-specific promoter or a combination thereof, for the treatment of hepatic fibrosis in a human and a pharmaceutically acceptable carrier, wherein the therapeutic protein is human MMP-1.

Baker teaches preparation of an adenoviral vector containing the gene sequence of MMP-9 under the control of CMV promoter (abstract, p. 385). Baker further teaches that increased

secretion of MMPs is implicated in many pathological conditions, including rheumatoid arthritis, restenosis and atherosclerosis etc. "Clear definition of the normal and pathological function of individual MMPs will benefit from approaches that use gene transfer to produce increases in MMP levels that mimic those observed in pathological conditions" (e.g. abstract).

Baker does not teach the dose of $1x10^7$ pfu to $1x10^{14}$ pfu and the nucleotide sequence encoding human MMP-1 protein.

Brincherhoff discloses a cDNA sequence of 2.1 kb encoding a human collagenase, which is human MMP-1 (e.g. abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to generate a recombinant adenoviral vector expressing a MMP-1 protein under the control of CMV promoter with dose of $1x10^7$ pfu to $1x10^{14}$ pfu because Baker teaches infecting cells with multiplicity of infection (MOI) of 0, 3, 30, 100, 300 or 1000 pfu/cell and determining effective dose is routine optimization of a result-effective variable and is obvious to one of ordinary skill and it would be obvious to one of ordinary skill to substitute the gene sequence of MMP-9 as taught by Baker with the cDNA sequence of human MMP-1 as taught by Brinckerhoff because they both are members of MMP family.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to obtain effective dose to optimize the effect of the recombinant adenoviral vector and to use gene transfer to produce increases in MMP levels that mimic those observed in pathological conditions as taught by Baker with reasonable expectation of success.

12. Claims 22 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al., 1996 (Matrix Biology, Vol. 15, pp. 383-395) in view of Melton et al., 2004 (US Patent No. 6,686,198 B1).

Claims 22 and 30 are directed to a pharmaceutical composition comprising a therapeutically effective amount of unitary doses of about $1x10^7$ pfu to $1x10^{14}$ pfu viral particles of recombinant adenoviral vectors containing a DNA sequence encoding a therapeutic protein under the control of a ubiquitous promoter, a tissue-specific promoter or a combination thereof, for the treatment of hepatic fibrosis in a human and a pharmaceutically acceptable carrier, wherein the therapeutic protein is a truncated receptor for TCF-beta type II.

Baker teaches preparation of an adenoviral vector containing the gene sequence of MMP-9 under the control of CMV promoter (abstract, p. 385). Baker further teaches that increased secretion of MMPs is implicated in many pathological conditions, including rheumatoid arthritis, restenosis and atherosclerosis etc. "Clear definition of the normal and pathological function of individual MMPs will benefit from approaches that use gene transfer to produce increases in MMP levels that mimic those observed in pathological conditions" (e.g. abstract).

Baker does not teach the dose of $1x10^7$ pfu to $1x10^{14}$ pfu and the nucleotide sequence encoding truncated receptor for TGF beta II protein.

Melton teaches preparation of an adenoviral vector expressing truncated receptor for a growth factor of the TGF-beta family, including soluble or membrane bound dominant negative receptors, for gene delivery in gene therapy (e.g. column 4, lines 13-26, column 16, last paragraph).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to generate a recombinant adenoviral vector expressing a truncated receptor for TGF beta II protein under the control of CMV promoter with dose of $1x10^7$ pfu to $1x10^{14}$ pfu because Baker teaches infecting cells with multiplicity of infection (MOI) of 0, 3, 30, 100, 300 or 1000 pfu/cell and determining effective dose is routine optimization of a result-effective variable and is obvious to one of ordinary skill and it would be obvious to one of ordinary skill to substitute the gene sequence of MMP-9 as taught by Baker with the cDNA sequence of truncated receptor of TGF beta II as taught by Melton because they both encode protein sequences.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to obtain effective dose to optimize the effect of the recombinant adenoviral vector and for gene delivery of DNA sequence encoding the truncated receptor of TGF beta family in gene therapy as taught by Melton with reasonable expectation of success.

13. Claims 22 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al., 1996 (Matrix Biology, Vol. 15, pp. 383-395) in view of Devarajan et al., 1992 (The Journal of Biological Chemistry, Vol. 267, No. 35, p. 25228-25232).

Claims 22 and 32 are directed to a pharmaceutical composition comprising a therapeutically effective amount of unitary doses of about $1x10^7$ pfu to $1x10^{14}$ pfu viral particles of recombinant adenoviral vectors containing a DNA sequence encoding a therapeutic protein under the control of a ubiquitous promoter, a tissue-specific promoter or a combination thereof, for the treatment of hepatic fibrosis in a human and a pharmaceutically acceptable carrier, wherein the therapeutic protein is human MMP-2.

Baker teaches preparation of an adenoviral vector containing the gene sequence of MMP-9 under the control of CMV promoter (abstract, p. 385). Baker further teaches that increased secretion of MMPs is implicated in many pathological conditions, including rheumatoid arthritis, restenosis and atherosclerosis etc. "Clear definition of the normal and pathological function of individual MMPs will benefit from approaches that use gene transfer to produce increases in MMP levels that mimic those observed in pathological conditions" (e.g. abstract).

Baker does not teach the dose of $1x10^7$ pfu to $1x10^{14}$ pfu and the nucleotide sequence encoding human MMP-2 protein.

Davarajan discloses a cDNA sequence encoding a human neutrophil gelatinase (HNG), which is human MMP-2 (e.g. abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to generate a recombinant adenoviral vector expressing a MMP-2 protein under the control of CMV promoter with dose of $1x10^7$ pfu to $1x10^{14}$ pfu because Baker teaches infecting cells with multiplicity of infection (MOI) of 0, 3, 30, 100, 300 or 1000 pfu/cell and determining effective dose is routine optimization of a result-effective variable and is obvious to one of ordinary skill and it would be obvious to one of ordinary skill to substitute the gene sequence of MMP-9 as taught by Baker with the cDNA sequence of human MMP-2 as taught by Davarajan because they both are members of MMP family.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to obtain effective dose to optimize the effect of the recombinant adenoviral vector and to use gene transfer to produce increases in MMP levels that mimic those observed in pathological conditions as taught by Baker with reasonable expectation of success.

14. Claims 22 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al., 1996 (Matrix Biology, Vol. 15, pp. 383-395) in view of Freije et al., 1994 (Journal of Biological Chemistry, Vol. 269, No. 24, p. 16766-16773).

Claims 22 and 34 are directed to a pharmaceutical composition comprising a therapeutically effective amount of unitary doses of about $1x10^7$ pfu to $1x10^{14}$ pfu viral particles of recombinant adenoviral vectors containing a DNA sequence encoding a therapeutic protein under the control of a ubiquitous promoter, a tissue-specific promoter or a combination thereof, for the treatment of hepatic fibrosis in a human and a pharmaceutically acceptable carrier, wherein the therapeutic protein is human MMP-13.

Baker teaches preparation of an adenoviral vector containing the gene sequence of MMP-9 under the control of CMV promoter (abstract, p. 385). Baker further teaches that increased secretion of MMPs is implicated in many pathological conditions, including rheumatoid arthritis, restenosis and atherosclerosis etc. "Clear definition of the normal and pathological function of individual MMPs will benefit from approaches that use gene transfer to produce increases in MMP levels that mimic those observed in pathological conditions" (e.g. abstract).

Baker does not teach the dose of $1x10^7$ pfu to $1x10^{14}$ pfu and the nucleotide sequence encoding human MMP-13 protein.

Freije discloses a cDNA sequence encoding collagenase-3, a novel human matrix metalloproteinase that is human MMP-13 (e.g. abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to generate a recombinant adenoviral vector expressing a MMP-13 protein under

the control of CMV promoter with dose of $1x10^7$ pfu to $1x10^{14}$ pfu because Baker teaches infecting cells with multiplicity of infection (MOI) of 0, 3, 30, 100, 300 or 1000 pfu/cell and determining effective dose is routine optimization of a result-effective variable and is obvious to one of ordinary skill and it would be obvious to one of ordinary skill to substitute the gene sequence of MMP-9 as taught by Baker with the cDNA sequence of human MMP-13 as taught by Freije because they both are members of MMP family.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to obtain effective dose to optimize the effect of the recombinant adenoviral vector and to use gene transfer to produce increases in MMP levels that mimic those observed in pathological conditions as taught by Baker with reasonable expectation of success.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Shin-Lin Chen/
Primary Examiner, Art Unit 1632